

REVIEW ARTICLE

What is the value of faster acting prandial insulin? Focus on ultra rapid lispro

Tim Heise MD¹  | Carolina Piras de Oliveira MD² | Rattan Juneja MD² | Anderson Ribeiro MD² | Farai Chigutsa MPH² | Thomas Blevins MD³ 

¹Profil, Neuss, Germany

²Eli Lilly and Company, Indianapolis, Indiana

³Texas Diabetes & Endocrinology, Austin, Texas

Correspondence

Thomas Blevins MD, Texas Diabetes & Endocrinology, Austin, TX 78731-4309.
Email: tblevins@texasdiabetes.com

Funding information

Eli Lilly and Company

Abstract

Rapid-acting insulins (RAIs) have been instrumental in the management of diabetes because of their improved postprandial glucose (PPG) control compared with regular human insulin. However, their absorption rate and time action following subcutaneous administration still falls short of the normal physiological response to meal consumption, increasing the risk of early postmeal hyperglycaemia and late postmeal hypoglycaemia. Increased demand for faster acting insulins, which can quickly control PPG excursions without increasing the risk of late hypoglycaemia, led to the development of ultra-rapid-acting insulins, including ultra-rapid lispro (URLi). URLi is a novel formulation of insulin lispro with accelerated absorption driven by two excipients: treprostinil, which increases local vasodilation, and citrate, which increases local vascular permeability. Clinical pharmacology studies consistently showed an earlier onset and shorter duration of action with URLi compared with Lispro. In a head-to-head study with Faster aspart, Aspart and Lispro, URLi was absorbed faster, provided earlier insulin action, and more closely matched physiological glucose response than the other insulins tested. URLi's unique pharmacokinetic properties increase its potential for improved PPG control beyond that achieved with RAIs. Indeed, in pivotal phase 3 trials, URLi was superior to Lispro for PPG control both at 1 and 2 hours after a meal in type 1 and type 2 diabetes with multiple daily injections, and in type 1 diabetes with continuous subcutaneous insulin infusion. This was achieved without increasing the risk of hypoglycaemia. In this review, we focus on the clinical and pharmacological evidence for URLi in the treatment of diabetes and discuss the potential benefits and considerations with URLi compared with RAIs.

KEYWORDS

glycaemic control, insulin analogues, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

Over the last century, insulin therapy has advanced from crude pancreatic extracts to recombinant DNA-based insulin analogues, which

more effectively mimic the basal insulin response between meals and the rapid insulin response after meals in people without diabetes (PwOD). Despite the availability of many basal and mealtime insulin analogues, a significant number of people with diabetes (PwD) still fail

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 Eli Lilly and Company. *Diabetes, Obesity and Metabolism* published by John Wiley & Sons Ltd.

to achieve glycaemic goals.¹⁻³ The complexity of insulin regimens is one reason for this. Regimens can include multiple injections per day, more than one type of insulin, and specific recommendations for the timing of prandial insulin administration to match the glucose content from meals with insulin concentration in the blood. Appropriate and recommended timing of insulin injection in relation to the meal can be challenging. Because of a delayed insulin response relative to the rapid absorption of glucose from meals, rapid-acting insulins (RAIs) such as insulin lispro (Lispro; Humalog; Eli Lilly and Company) and insulin aspart (Aspart; Novolog; Novo Nordisk) should optimally be given within 15 minutes prior to a meal, while regular insulin (Humulin; Eli Lilly and Company), the first synthetic human insulin, should be injected 30 minutes prior to meal consumption. The need to administer the insulin significantly in advance of a meal can be challenging for PwD.^{4,5} Taking these insulins too early before a meal can lead to hypoglycaemia and defaulting to taking the insulin just before or after a meal can lead to postmeal hyperglycaemia. Faster acting insulins that can decrease the time between insulin administration and action could allow the insulin to be administered closer to the meal-time and hence reduce the risk associated with inadvertent untimely dosing.

One of the primary limiting factors for exogenous insulin response is the rate of absorption into the capillaries from the subcutaneous space. For this reason, recent RAI analogue development has involved finding approaches to speed up insulin absorption.

2 | EVOLUTION FROM RAI ANALOGUES TO ULTRA-RAPID-ACTING INSULINS

Over the years, increased demand from healthcare providers and PwD for faster acting insulins that improve glycaemic control has spurred on the development of faster acting RAI analogues.⁶ RAIs are recombinant therapeutic agents with modifications to the amino acid chain versus endogenous human insulin. The first RAI, Lispro, was first approved in 1996. In Lispro, the placement of the amino acids lysine and proline was switched, allowing the insulin to rapidly dissociate from its hexameric structure into monomers following subcutaneous injection.⁷ This shortened the onset of action after subcutaneous injection and allowed PwD to inject their insulin 15-20 minutes before a meal with Lispro compared with 30-40 minutes premeal with regular human insulin. Two other analogue mealtime insulins, Aspart and insulin glulisine (Glulisine; Apidra; Sanofi), were subsequently introduced.

Currently, the quality of glycaemic control is not only indicated by HbA1c, but also by continuous glucose monitoring (CGM) metrics such as time in range (TIR), time below range (TBR) and time above range (TAR), which help to elucidate potential areas for glycaemic improvement.⁸⁻¹⁰ Postprandial glucose (PPG) is known to have a significant impact on both HbA1c and TIR in people with type 1 or type 2 diabetes.¹¹⁻¹⁴ Inadequately controlled PPG, such as early postprandial hyperglycaemia and late postprandial hypoglycaemia, is associated with unfavourable clinical outcomes for PwD.¹⁵⁻¹⁷ While a direct causal relationship between improvement in PPG control and clinical

outcomes has not been established in clinical trials, consistently high PPG has been associated with microvascular and macrovascular disease, retinopathy and, in older people with type 2 diabetes, impaired cognitive function.¹⁸⁻²³ In recognition of these possible outcomes, guidelines recommend more TIR and less TBR and TAR, which can be achieved with medications that enable better PPG control.^{18,24-26}

One approach to address PPG control is to speed up the pharmacokinetics (PK) of the mealtime insulin to facilitate a more rapid onset and shorter duration of action. To that end, several efforts have been made towards developing such insulins, including faster acting insulin aspart (Faster aspart; Fiasp; Novo Nordisk), which was approved by the U.S. Food and Drug Administration in 2017, and ultra-rapid lispro (URLi; Lyumjev; Eli Lilly and Company), which was approved in 2020.

URLi is a novel formulation of insulin lispro, developed to more closely match the body's physiological insulin response to a meal, thereby improving PPG control. It contains two enabling excipients, citrate and treprostinil, which accelerate insulin absorption beyond that achieved by Lispro. In preclinical and phase 1 studies, injection of citrate into subcutaneous tissue resulted in a localized increase in vascular permeability, while micro doses of treprostinil caused localized vasodilation without exhibiting systemic effects or being detected in plasma.²⁷⁻²⁹

3 | PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE OF URLI

The pharmacokinetic (PK) and pharmacodynamic (PD) properties of URLi have been characterized in a number of phase 1 trials. Most of these were single-dose, randomized, double-blind, crossover studies comparing the PK/PD of URLi with Lispro following single-dose subcutaneous injection in PwD, people with type 1 diabetes or people with type 2 diabetes. PK/PD were also assessed following continuous subcutaneous insulin infusion (CSII) in people with type 1 diabetes. Key findings from the completed trials are summarized in the following sections.

3.1 | PK/PD of URLi compared with Lispro

3.1.1 | Subcutaneous injection

A pooled analysis of the PK and PD of URLi across different population groups has been published.³⁰ The analysis included four randomized, double-blind, crossover, single-dose studies (PwD [n = 74], people with type 1 diabetes [n = 78] and type 2 diabetes [n = 38]) evaluating subcutaneous doses of URLi and Lispro during an 8- to 10-hour euglycaemic clamp procedure.

Following subcutaneous injection, URLi was absorbed more rapidly, showing reduced late exposure and a shorter duration of action compared with Lispro (Table 1). URLi showed 5-minute faster onset of appearance in serum, an ~8-fold greater exposure in the first 15 minutes, and a 43% reduction in exposure beyond 3 hours compared with Lispro across all study populations and dose ranges (Table 1).

TABLE 1 Treatment difference and ratio of geometric least squares means between URLi and Lispro for pharmacokinetic variables and insulin action following subcutaneous injection in people with diabetes in the pooled analysis set

	Treatment difference (95% confidence interval)	Treatment ratio (95% confidence interval)
Pharmacokinetics		
Onset of appearance (min)	-4.75 (-5.38, -4.12)	-
Early 50% t_{max} (min)	-13.98 (-15.22, -12.73)	-
Late 50% t_{max} (min)	-17.58 (-23.31, -11.86)	-
Duration of exposure (min)	-68.19 (-76.96, -59.53)	-
T_{max} (min)	0.01 (-0.07, 0.09)	-
C_{max}	-	1.14 (1.11, 1.18)
$AUC_{0-15min}$	-	7.51 (6.63, 8.51)
AUC_{0-1h}	-	1.52 (1.45, 1.59)
AUC_{3h-Xh}	-	0.57 (0.53, 0.60)
$AUC_{0-\infty}$	-	1.03 (1.01, 1.05)
Insulin action		
T_{Onset} (min)	-10.33 (-12.01, -8.64)	-
Early 50% t_{Rmax} (min)	-12.31 (-14.84, -9.78)	-
Late 50% t_{Rmax} (min)	-37.94 (-45.40, -30.47)	-
Duration of action (min)	-43.81 (-58.60, -29.02)	-
$Gtot_{0-30min}$	-	3.07 (2.72, 3.50)
$Gtot_{0-1h}$	-	1.73 (1.64, 1.84)
$Gtot_{4h-end}$	-	0.65 (0.61, 0.70)
$Gtot$	-	0.99 (0.95, 1.02)
$Rmax$	-	1.12 (1.08, 1.16)

Note. For variables with at least one participant with a value of 0, treatment ratios of least-squares means and their 95% CIs were estimated using Fieller's method.

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-15min}$, AUC from 0 to 15 minutes; AUC_{0-1h} , AUC from 0 to 1 hours; AUC_{3h-Xh} , AUC from 3 to X hours; $AUC_{0-\infty}$, AUC from time 0 to infinity; C_{max} , maximum observed drug concentration; early 50% t_{max} , time to early half-maximal drug concentration; early 50% t_{Rmax} , time to half-maximal glucose infusion rate before maximum glucose infusion rate; $Gtot$, total amount of glucose infused over the duration of the clamp procedure; $Gtot_{0-30min}$, total amount of glucose infused over 30 minutes; $Gtot_{0-1h}$, total amount of glucose infused over 1 hour; $Gtot_{4h-end}$, total amount of glucose infused from 4 hours postdose until the end of the clamp; late 50% t_{Rmax} , time to half-maximal glucose infusion rate after maximum glucose infusion rate; late 50% t_{max} , time to late half maximal drug concentration; $Rmax$, maximum glucose infusion rate; T_{max} , time to maximum observed drug concentration; T_{Onset} , time to onset of insulin action; URLi, ultra-rapid lispro.

In line with URLi's accelerated PK, an earlier glucose-lowering effect and reduced late glucose-lowering was shown. Compared with Lispro, URLi had a 10-minute faster onset of action, 3-fold greater insulin action in the first 30 minutes, and a 35% reduction in insulin action beyond 4 hours across all populations and dose ranges (Table 1).

Further studies were conducted to determine the PK/PD of URLi and Lispro following multiple daily injections (MDI) in type 1 and type 2 diabetes.^{31,32} Differences in PK and glucose response between URLi and Lispro were sustained after multiple daily subcutaneous dosing in both type 1 and type 2 diabetes.

3.1.2 | Glucodynamics at different meal-to-dose timing

A six-period crossover design was used to compare the PPG response to a solid meal test with URLi or Lispro dosed at -15, 0 and +15

minutes relative to the start of the meal among people with type 1 and type 2 diabetes.^{31,32} The meal was provided as a typical continental breakfast and individualized for each participant. It contained 30% of the calories needed per day for weight maintenance, with macronutrients targeted to provide 50% of the calories from carbohydrate, 30% from fat and 20% from protein.

Overall, URLi resulted in lower PPG excursions compared with Lispro when dosed before, at, or after the meal test in both type 1 and type 2 diabetes^{31,32} (Table 2). Importantly, there was no significant difference between treatments when URLi was administered at mealtime (time 0) compared with Lispro before meals (time -15 minutes).

3.1.3 | Continuous subcutaneous insulin infusion

The PK/PD profiles of URLi and Lispro following CSII were evaluated in adults with type 1 diabetes.³³ URLi had similar overall exposure but

TABLE 2 Pharmacodynamic variables following administration of URLi compared with Lispro at different meal-to-dose timing in people with type 1 or type 2 diabetes

Variable	Time comparison ^a URLi vs. Lispro	URLi LSM (N)	Lispro LSM (N)	Ratio ^b of LSM URLi: Lispro (90% confidence interval)
Type 1 diabetes				
ΔAUC_{0-5h} (mg h/dl)	(-15 min) vs. (-15 min)	55.77 (27)	92.27 (28)	0.60 (0.03, 1.15)
	(0 min) vs. (0 min)	76.37 (27)	135.54 (29)	0.56 (0.21, 1.04)*
	(+15 min) vs. (+15 min)	106.38 (29)	184.37 (29)	0.58 (0.38, 0.87)*
	(0 min) vs. (-15 min)	76.37 (27)	92.27 (28)	0.83 (0.39, 1.36)
Type 2 diabetes				
ΔAUC_{0-5h} (mg h/dl)	(-15 min) vs. (-15 min)	46.96 (26)	91.85 (29)	0.51 (0.14, 0.85)*
	(0 min) vs. (0 min)	-5.51 (28)	120.21 (30)	-0.05 (-0.40, 0.18)***
	(+15 min) vs. (+15 min)	98.72 (29)	138.15 (28)	0.71 (0.52, 0.92)*
	(0 min) vs. (-15 min)	-5.51 (28)	91.85 (29)	-0.06 (-0.60, 0.22)***

Abbreviations: AUC, area under the concentration versus time curve; $\Delta AUC_{(0-5h)}$, change from baseline in AUC from time 0 to 5 hours; LSM, least squares mean; N, number of participants; URLi, ultra-rapid lispro.

* $P < .1$ (prespecified significance level). *** $P < .0001$. ^aTime comparison refers to time of administration of insulin relative to the mealtime: 15 minutes before (-15 min), at the time of the meal (0 min) and 15 minutes after the start of the meal (+15 min).

^bConfidence intervals (CIs) were calculated using Fieller's Theorem.

accelerated serum insulin lispro absorption compared with Lispro using either a standard single-wave (SS) or standard dual-wave (SD) bolus on both days 1 and 3.³³ URLi showed a significantly earlier glucose-lowering effect and a trend towards lower PPG excursions over the complete 5-hour meal test compared with Lispro using either SS or SD bolus.

3.2 | PK/PD of URLi compared with other RAIs

The pharmacological properties following a single subcutaneous injection of URLi, Lispro, Aspart and Faster aspart were characterized in people with type 1 diabetes in a phase 1, randomized, double-blind, four-period crossover study.³⁴ Participants received the same individualized subcutaneous dose of each study drug immediately prior to a liquid meal test, which consisted of 100 g of carbohydrates, 26 g of protein and 22 g of fat (16 fl/oz liquid Ensure Plus; Abbott Laboratories, Abbott Park, IL). For comparison, 12 PwOD received the same test meal.

3.2.1 | Pharmacokinetics

Upon comparing the insulin concentration-time profiles, URLi and Faster aspart showed earlier onset of appearance in serum and reduced late exposure compared with Lispro and Aspart, respectively, indicating comparatively faster absorption and shorter duration of action of the faster acting insulins (Figure 1A,B).

Further to this, URLi showed significantly faster insulin absorption than all the other insulins tested (Figure 1A). Early 50% t_{max} was reached 12.8 minutes after URLi administration, which was 5.9 minutes faster than Faster aspart, 12.5 minutes faster than Lispro and

13.9 minutes faster than Aspart (all $P < .0001$; Table 3). This accelerated insulin absorption with URLi resulted in significantly greater early insulin exposure: insulin exposure during the first 15 minutes ($AUC_{0-15min}$) increased with URLi by 1.5-fold versus Faster aspart, 5-fold versus Lispro and 5-fold versus Aspart (Table 3). In line with the leftward shift of the concentration-time curve, late insulin exposure after URLi administration was significantly reduced compared with all the insulins tested (Figure 1B). Insulin exposure beyond 3 hours (AUC_{3-7h}) after URLi administration was reduced by 54% compared with Faster aspart, 49% compared with Lispro and 61% compared with Aspart (all $P < .0001$; Table 3). Late 50% t_{max} occurred 9.5 minutes later with Faster aspart, 13.8 minutes later with Lispro and 21.1 minutes later with Aspart compared with URLi (all $P < .05$).

3.2.2 | Pharmacodynamics

URLi and Faster aspart resulted in lower glucose excursions in the first 4 hours after the meal test compared with Lispro and Aspart, respectively, indicating improved PPG control with the faster acting insulins (Figure 1C). Overall, URLi showed the lowest mean glucose excursion during the test meal compared with Faster aspart, Lispro and Aspart (Figure 1C).

URLi had a numerically greater glucose-lowering effect compared with all the insulins tested, with a statistically significant improvement in PPG excursions over the first 5 hours compared with Lispro and Aspart (Table 4). The maximum PPG excursion (ΔBG_{max}) and excursions at 1 (ΔBG_{1h}) and 2 hours (ΔBG_{2h}) postmeal were also significantly reduced with URLi compared with Lispro and Aspart (all $P < .05$, Table 4) and were numerically reduced compared with Faster aspart. At 2 hours postmeal, URLi achieved the greatest numerical reduction in PPG values compared with Faster aspart, Lispro and Aspart, with

Pharmacokinetic and pharmacodynamic results for URLi, Faster aspart, Lispro and Aspart

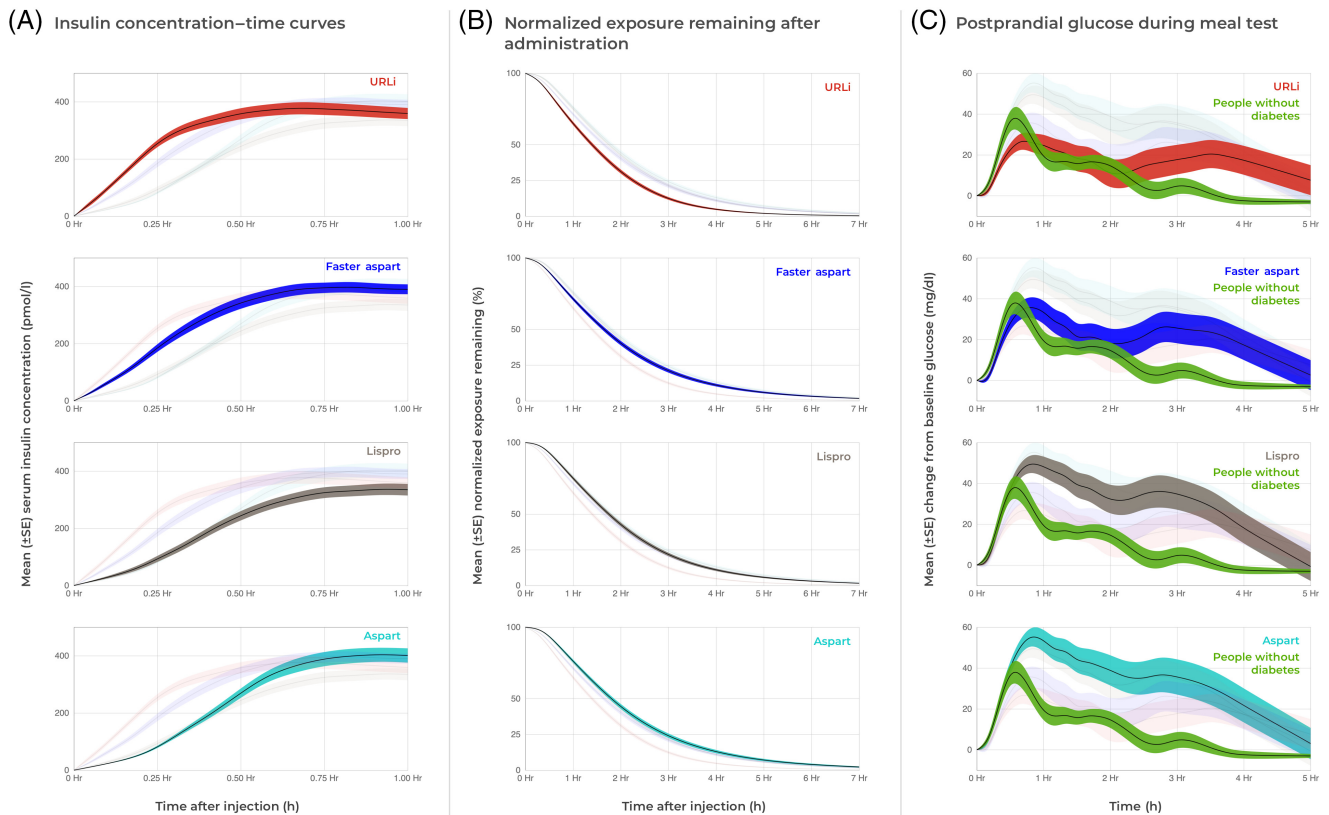


FIGURE 1 Pharmacokinetic and pharmacodynamic profiles of faster aspart, Aspart, Lispro and URLi following a meal test in adults with type 1 diabetes. A, Mean insulin concentration (\pm standard error [SE]) versus time in the first hour postinjection, B, Mean normalized exposure remaining (\pm SE) versus time from 0 to 7 hours postinjection, and C, Mean (\pm SE) change from baseline glucose concentration versus time postmeal. Mean data are shown as a solid black line and SE as a shaded area for the named insulin; other insulins are shown in the background for comparison. URLi, ultra-rapid lispro

differences reaching statistical significance when compared with Lispro and Aspart (Table 4). In addition, the 2-hour PPG value with URLi was closest to that in PwD compared with other insulins tested (Figure 1C). In fact, glucose excursions over the first 3 hours postmeal with URLi were more comparable with those in PwD than the other insulins tested (Figure 1C).

3.3 | PK/PD summary

- URLi showed an accelerated PK/PD profile compared with Lispro across all studies, showing faster absorption, increased early insulin exposure and reduced late insulin exposure with both subcutaneous injection and CSII administration.
- Compared with Faster aspart, Lispro and Aspart
 - URLi showed the fastest insulin absorption, greatest early insulin exposure and lowest late insulin exposure.
 - URLi achieved the greatest numerical reduction in PPG at 2 hours postmeal.
 - Glucose excursions over the first 3 hours postmeal with URLi were more comparable with those in healthy subjects.

- URLi improved PPG control compared with other RAIs.
- URLi's PK/PD profile provides an opportunity for administration at the start of the meal with greater subsequent glycaemic control and reduced risk of late postmeal hypoglycaemia.

4 | EFFICACY OVERVIEW

The efficacy and safety of URLi were evaluated in three pivotal phase 3 trials encompassing 2327 participants. The findings from these trials are discussed in the following sections.

4.1 | MDI in type 1 diabetes

PRONTO-T1D was a phase 3, randomized, treat-to-target, multinational study evaluating the efficacy and safety of URLi versus Lispro among 1222 adults with type 1 diabetes.³⁵ Participants were randomized to 26 weeks of double-blind URLi or Lispro, administered 0-2 minutes prior to meals (mealtime) as part of a basal-bolus regimen with insulin glargine or degludec. A third, open-label arm was included

TABLE 3 Pharmacokinetic variables following administration of ultra-rapid lispro (URLi), Lispro, faster aspart and Aspart in people with type 1 diabetes

Variable	Comparison	LSM difference (95% CI)	Ratio of geometric LSM (95% CI)
Early 50% t_{max} (min)	URLi – Lispro	–12.5 (–14.3, –10.8)***	–
	URLi – faster aspart	–5.86 (–7.65, –4.06)***	–
	URLi – Aspart	–13.9 (–15.7, –12.1)***	–
AUC _{0-15min}	URLi – Lispro	–	5.11 (3.96, 6.58)***
	URLi – faster aspart	–	1.48 (1.16, 1.90)**
	URLi – Aspart	–	5.25 (4.11, 6.71)***
AUC _{0-30min}	URLi – Lispro	–	2.85 (2.37, 3.43)***
	URLi – faster aspart	–	1.23 (1.02, 1.48)*
	URLi – Aspart	–	2.38 (1.98, 2.87)***
Late 50% t_{max} (min)	URLi – Lispro	–13.8 (–23.0, –4.57)**	–
	URLi – faster aspart	–9.54 (–18.8, –0.329)*	–
	URLi – Aspart	–21.1 (–30.3, –11.9)***	–
Duration (min)	URLi – Lispro	–46.7 (–62.3, –31.1)***	–
	URLi – faster aspart	–45.2 (–61.4, –28.9)***	–
	URLi – Aspart	–50.1 (–67.7, –32.5)***	–
T_{max} (min)	URLi – Lispro	–0.146 (–0.242, –0.050)**	–
	URLi – faster aspart	0.0135 (–0.082, 0.110)	–
	URLi – Aspart	–0.122 (–0.219, –0.026)*	–
AUC _{3-7h}	URLi – Lispro	–	0.507 (0.439, 0.586)***
	URLi – faster aspart	–	0.460 (0.398, 0.532)***
	URLi – Aspart	–	0.390 (0.337, 0.450)***
C_{max}	URLi – Lispro	–	1.13 (1.05, 1.22)**
	URLi – faster aspart	–	0.926 (0.861, 0.996)*
	URLi – Aspart	–	0.943 (0.877, 1.01)
AUC _{0-∞}	URLi – Lispro	–	1.03 (0.972, 1.09)
	URLi – faster aspart	–	0.835 (0.789, 0.883)***
	URLi – Aspart	–	0.821 (0.776, 0.868)***

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-15min}, AUC from 0 to 15 min; AUC_{0-30min}, AUC from 0 to 30 min; AUC_{3-7h}, AUC from 3 h to 7 hours; AUC_{0-∞}, AUC from 0 to infinity; C_{max}, maximum observed drug concentration; early 50% t_{max} , time to early half-maximal drug concentration; late 50% t_{max} , time to late half-maximal drug concentration; LSM, least squares mean; t_{max} , time to maximum observed drug concentration. * $P < .05$. ** $P < .01$. *** $P < .0001$.

to assess efficacy with postmeal administration of URLi given 20 minutes after the start of the meal. The primary endpoint was non-inferiority of URLi to Lispro in change from baseline HbA_{1c}. A 4-hour liquid meal test (Ensure Plus or similar country option with a nutrient composition of ~700 calories and 100 g of carbohydrate) was performed at baseline and week 26. An additional 26-week treatment phase evaluating long-term efficacy and safety was also conducted.³⁶

Mealtime URLi showed non-inferiority to Lispro for change in HbA_{1c} from baseline to week 26 (Table 5). Postmeal administration of URLi was also non-inferior to Lispro but resulted in a significantly higher endpoint HbA_{1c} ($P < .05$).

Mealtime URLi showed superiority to Lispro in controlling both 1- and 2-hour PPG excursions (Table 5) and resulted in significantly lower PPG excursions from 15 minutes to 4 hours after starting the meal test (Figure 2). Postmeal URLi resulted in significantly higher excursions compared with Lispro in the first hour after the start of the meal, but excursions were numerically lower than Lispro from 2 hours

postmeal and beyond. The incremental area under the serum glucose concentration-time curve from 0 to 4 hours (iAUC_{0-4 h}) was significantly lower in the mealtime URLi versus the Lispro group (estimated treatment difference [ETD] –5827.6 mg min/dl [95% CI –7701.0, –3954.1]; $P < .001$).

Significantly lower self-monitored blood glucose (SMBG) values were observed with mealtime URLi compared with Lispro at the morning 1-hour postmeal (166.9 vs. 180.6 mg/dl) and 2-hour postmeal time points (152.9 vs. 164.5 mg/dl), showing continued improvement in PPG control with URLi in the ambulatory setting. Overall glycaemic control and improved PPG via SMBG were maintained after 52 weeks with mealtime URLi, showing that the efficacy of URLi was preserved during long-term treatment in people with type 1 diabetes.³⁶

Blinded CGM was used by a subset of participants enrolled in PRONTO-T1D for up to 14 days before baseline and the 26-week primary endpoint.³⁷ Mealtime URLi was superior to Lispro in reducing

TABLE 4 Pharmacodynamic variables following administration of URLi, Lispro, faster aspart and Aspart in people with type 1 diabetes

Variable	Treatment	LSM	Comparison	LSM difference ^a (95% CI)
Glucose Δ AUC(0-5 h) (mg h/dl)	URLi	109.72	–	–
	Lispro	181.57	URLi – Lispro	–71.85 (–131.54, –12.15)*
	Faster aspart	127.50	URLi – faster aspart	–17.78 (–76.67, 41.12)
	Aspart	200.60	URLi – Aspart	–90.87 (–150.25, –31.49)**
Δ BG _{max} (mg/dl)	URLi	64.78	–	–
	Lispro	77.89	URLi – Lispro	–13.12 (–26.18, –0.05)*
	Faster aspart	70.39	URLi – faster aspart	–5.61 (–18.68, 7.45)
	Aspart	86.55	URLi – Aspart	–21.77 (–34.83, –8.70)**
Δ BG _{1h} (mg/dl)	URLi	25.17	–	–
	Lispro	48.19	URLi – Lispro	–23.01 (–34.12, –11.91)***
	Faster aspart	33.91	URLi – faster aspart	–8.74 (–19.84, 2.37)
	Aspart	53.66	URLi – Aspart	–28.48 (–39.64, –17.33)***
Δ BG _{2h} (mg/dl)	URLi	10.64	–	–
	Lispro	31.67	URLi – Lispro	–21.03 (–35.90, –6.15)**
	Faster aspart	17.73	URLi – faster aspart	–7.08 (–21.96, 7.80)
	Aspart	39.57	URLi – Aspart	–28.93 (–43.87, –13.98)**

Abbreviations: Δ BG_{1h}, change from baseline glucose at 1 hour; Δ BG_{2h}, change from baseline glucose at 2 hours; Δ BG_{max}, maximum change from baseline glucose value; CI, confidence interval; glucose Δ AUC(0-5 h), change from baseline glucose area under the concentration versus time curve from time 0 to 5 hours postmeal; LSM, least squares mean; URLi, ultra-rapid lispro.

Model: glucodynamics = period + treatment + sequence + participant (sequence) + random error, where participant (sequence) is fitted as a random effect.

* $P < .05$. ** $P < .01$. *** $P < .0001$. ^a P value is for the test of the mean difference.

breakfast i AUC_{0-2h} (ETD –28.1 mg h/L, $P = .048$) and i AUC_{0-2h} for all meals combined. Incremental AUC_{0-3h} and i AUC_{0-4h} were also significantly reduced with mealtime URLi for all meals combined. Postmeal URLi resulted in similar PPG control to mealtime Lispro, but less optimal PPG control compared with mealtime URLi. Mealtime URLi increased daytime TIR 71-180 mg/dl by 43.6 minutes ($P = .020$; 44.0 minutes when TIR was 70-180 mg/dl [$P = .020$]) and decreased night-time time in hypoglycaemia of 70 mg/dl or less by 11.5 minutes ($P = .009$) compared with mealtime Lispro. Mean glucose profiles over the 24-hour period showed lower blood glucose levels with mealtime URLi compared with Lispro during the daytime, but increasing levels from evening to early morning.³⁷

Findings in PRONTO-T1D showed that URLi provided good glycaemic control, with non-inferiority to lispro confirmed for both mealtime and postmeal URLi, while superior PPG control was shown with mealtime dosing of URLi. These results were supported by the PRONTO-T1D CGM substudy, which showed that mealtime URLi resulted in improved daytime time in the target range.

4.2 | MDI in type 2 diabetes

The efficacy and safety of URLi compared with Lispro was evaluated among 673 adults with type 2 diabetes in the phase 3, randomized, double-blind, treat-to-target, multicentre PRONTO-T2D study.³⁸ Participants were randomized to 26 weeks of double-blind URLi or Lispro, administered 0-2 minutes prior to meals as part of a basal-

bolus regimen with insulin glargine or degludec. Continuing metformin and/or a sodium-glucose co-transporter-2 inhibitor was permitted during the study. As with PRONTO-T1D, a liquid meal test was performed at baseline and week 26 to assess PPG control.

HbA1c improved in both treatment groups, and non-inferiority of URLi to Lispro was confirmed for change from baseline to week 26 (Table 5). At week 26, 58% of participants on URLi and 53% on Lispro treatment reached a target HbA1c of less than 7.0%, while 38% and 35%, respectively, achieved an HbA1c of 6.5% or less.

Similar to PRONTO-T1D, URLi was superior to Lispro in controlling 1- and 2-hour PPG excursions during the meal test (Table 5 and Figure 2). Significantly lower PPG excursions were evident from 30 minutes to 4 hours postmeal with URLi treatment.³⁸ Incremental AUC during the meal test was significantly lower in the URLi group at all time intervals during the 4-hour test at week 26. In addition, 10-point SMBG profile testing showed similar fasting glucose between URLi and Lispro, but lower morning 1-hour postmeal (168.4 vs. 180.4 mg/dl, respectively; $P < .001$) and 2-hour postmeal (153.8 vs. 169.3 mg/dl, respectively; $P < .001$) blood glucose values with URLi compared with Lispro.

4.3 | CSII in type 1 diabetes

Following demonstration of the compatibility and safety of URLi with CSII in the PRONTO-Pump study³⁹ (section 5.3), its efficacy with CSII administration was evaluated in the PRONTO-Pump-2 study.⁴⁰ Both studies used the Medtronic MiniMed insulin pump.

TABLE 5 Summary of key efficacy results from phase 3 clinical trials with URLi and Lispro in people with type 1 or type 2 diabetes

Trial	Treatment duration	Participant demographics at baseline	Intervention	Endpoint HbA1c, %	Primary HbA1c outcome (ETD URLi–Lispro [95% CI])	PPG outcome versus Lispro ^a , mg/dl (ETD URLi–Lispro [95% CI])
PRONTO-T1D	26 wk	1222 adults Type 1 diabetes Mean age = 44.4 y Mean HbA1c = 7.34%	Mealtime URLi	7.21	–0.08% (–0.16, 0.00)non-inferiority confirmed	1-h postmeal: –27.9 mg/dl (–35.3, –20.6)** [–1.55 mmol/L (–1.96, –1.14)] Superiority confirmed 2-h postmeal: –31.2 mg/dl (–41.1, –21.2)** [–1.73 mmol/L (–2.28, –1.18)] superiority confirmed
			Mealtime Lispro	7.29	–	–
			Postmeal URLi	7.42	+0.13% (0.04, 0.22)non-inferiority confirmed	1-h postmeal: 13.2 mg/dl (5.0, 21.4)* [0.73 mmol/L (0.28, 1.19)] 2-h postmeal: –6.7 mg/dl (–17.6, 4.3) [–0.37 mmol/L (–0.98, 0.24)]
PRONTO-T2D	26 wk	673 adults Type 2 diabetes Mean age = 60.6 y Mean HbA1c = 7.29%	Mealtime URLi	6.92	+0.06% (–0.05, 0.16)non-inferiority confirmed	1-h postmeal: –11.8 mg/dL (–18.1, –5.5)** [–0.66 mmol/L (–1.01, –0.30)]superiority confirmed 2-h postmeal: –17.4 mg/dL (–25.3, –9.5)** [–0.96 mmol/L (–1.41, –0.52)]superiority confirmed
			Mealtime Lispro	6.86	–	–
PRONTO-Pump-2	16 wk	432 adults Type 1 diabetes Mean age = 46.4 y Mean HbA1c = 7.55%	Mealtime URLi	7.48	+0.02% (–0.06, 0.11)non-inferiority confirmed	1-h postmeal: –24.1 mg/dl (–36.0, –12.2)** [–1.34 mmol/L (–2.00, –0.68)] superiority confirmed 2-h postmeal: –27.8 mg/dl (–42.6, –13.0)** [–1.54 mmol/L (–2.37, –0.72)] superiority confirmed
			Mealtime Lispro	7.46	–	–

Abbreviations: CI, confidence interval; ETD, estimated treatment difference; PPG, postprandial glucose; URLi, ultra-rapid lispro.

* $P < .05$. ** $P < .001$. ^aMain PPG outcome was PPG excursions at 1 and 2 hours after the meal test at week 26 for PRONTO-T1D and PRONTO-T2D, and PPG values at 1 and 2 hours after the meal test at week 16 for PRONTO-Pump-2.

PRONTO-Pump-2 was a phase 3, randomized, double-blind, multi-centre study, conducted in 432 adults with type 1 diabetes who were using CSII prior to the study. Participants were randomized to 16 weeks of treatment with URLi or Lispro delivered by CSII as both basal and bolus insulin, with bolus doses administered 0–2 minutes before meals.

Non-inferiority of URLi to Lispro was confirmed for change in HbA1c at week 16. URLi showed superiority to Lispro in controlling 1- and 2-hour PPG levels, with an ETD of –24.1 mg/dl (95% CI –36.0, –12.2) at 1 hour and –27.8 mg/dl (95% CI –42.6, –13.0) at 2 hours (both $P < .001$). Significantly lower PPG excursions were also shown (Table 5; Figure 2). Consistent with the meal test findings, postmeal $iAUC_{0-1h}$ and $iAUC_{0-2h}$ from CGM were significantly lower with URLi treatment for breakfast, lunch and dinner. Overall, URLi resulted in a significant reduction in postmeal $iAUC_{0-1h}$ and

$iAUC_{0-2h}$ of 45% and 37%, respectively, compared with Lispro. TIR (70–180 mg/dl) and time in hyperglycaemia were similar between groups, but URLi resulted in significantly less time in hypoglycaemia (<54 mg/dl) over the daytime, night-time and 24-hour period (ETD –0.41%, –0.97% and –0.52%, respectively, all $P < .05$). Similar to results in the PRONTO-T1D CGM substudy, ambulatory glucose profiles showed a trend towards increasing blood glucose levels between evening and morning hours with URLi treatment.

4.3.1 | Closed loop systems

With the evolving insulin delivery landscape, it is probable that more PwD will move towards hybrid or fully automated closed loop

URLi results in lower postprandial glucose excursions compared to Lispro

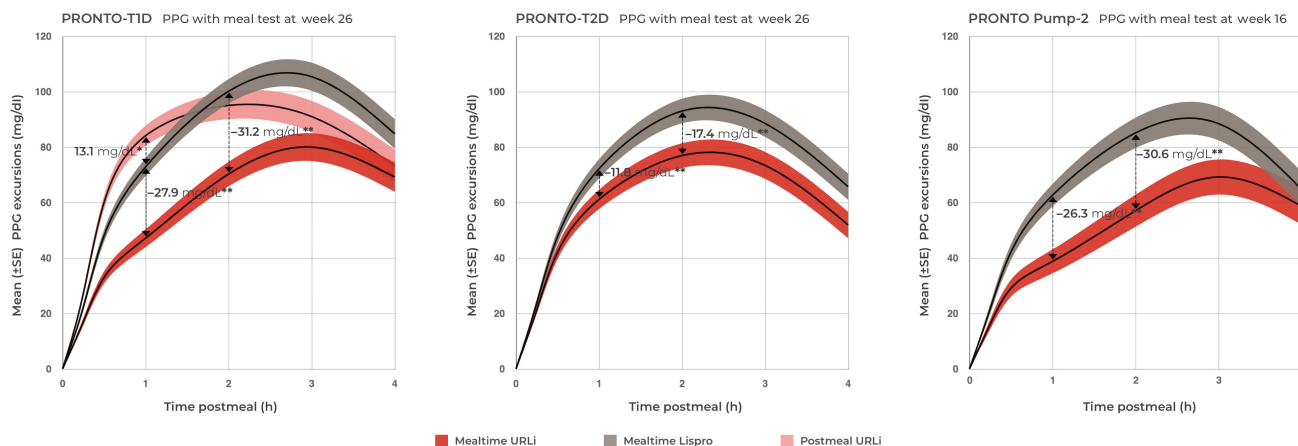


FIGURE 2 Mean postprandial glucose excursions following a meal test at study endpoint in PRONTO-T1D, PRONTO-T2D and PRONTO-Pump-2. PPG, postprandial glucose; URLi, ultra-rapid lispro. * $P < .05$, ** $P < .001$. Mean data are shown as a solid black line and standard error as a shaded area

systems. There is potential for improved glycaemic control with ultra-rapid insulins in these systems given their more effective PPG control. However, currently there is not enough evidence to support this.⁴¹⁻⁴⁴ It is probable that algorithms in these automated systems, which were developed for RAIs, will need to be optimized for the faster PK/PD properties of URLi.

4.4 | Efficacy summary

- Across studies, URLi showed non-inferiority to Lispro on reduction of HbA1c from baseline to endpoint.
- Mealtime URLi consistently showed superior PPG control in type 1 and type 2 diabetes with either MDI or CSII therapy.
- CGM analysis also showed significant improvements in postprandial and daytime glucose control with URLi treatment compared with Lispro.

5 | SAFETY AND TOLERABILITY

5.1 | Hypoglycaemia

The incidence and rate of severe hypoglycaemia with URLi treatment remained low and similar to Lispro across all studies (Table 6). Overall, rates of documented, nocturnal and non-nocturnal hypoglycaemia were lower with URLi treatment in type 1 diabetes, and marginally higher compared with Lispro in type 2 diabetes.

In the postprandial period, the rate of hypoglycaemia was consistently lower with URLi compared with Lispro during CSII, with differences reaching statistical significance in the timeframes of 2-4 hours and up to 4 hours after the start of the meal. With MDI, the rate of postmeal hypoglycaemia with URLi was consistent with its insulin

time action, with a numerically higher rate of hypoglycaemia compared with Lispro in the early postprandial period and a lower rate in the late postprandial period, corresponding to URLi's earlier onset and shorter duration of action. In PRONTO-T1D, a significantly lower rate of postmeal hypoglycaemia was observed with URLi beyond 4 hours after meals,³⁵ probably indicative of URLi's shorter duration of action. On the other hand, in PRONTO-T2D, a significantly higher rate of postmeal hypoglycaemia was seen with URLi treatment within the first 4 hours after meals,³⁸ in line with a quicker onset of action. This was similar to trends observed with Faster aspart.^{45,46}

5.2 | Adverse events

The incidence of serious adverse events was similar between URLi and Lispro across trials, with similar numbers of participants reporting hypoglycaemia between groups (Table 7).

A higher incidence of treatment-emergent injection or infusion site reactions was observed with URLi compared with Lispro (Table 7). With MDI therapy, most events were reported as injection site reaction or injection site pain (Table 7). Events were mostly mild or moderate in severity and resolved during the study, but one participant (0.3%) in the PRONTO-T2D study discontinued URLi treatment because of injection site reactions.

Infusion site reactions were numerically higher with both treatments during CSII therapy compared with MDI therapy (Table 7). Similar to MDI, the most frequently reported were infusion site reaction or infusion site pain. While the majority of events were reported as mild (~76%), seven participants (3.3%) discontinued URLi treatment because of infusion site reactions compared with none on Lispro treatment.

The cause of the higher incidence of injection or infusion site reactions with URLi is not entirely clear, although the increased localized vasodilation caused by treprostinil, or a local effect of citrate,

TABLE 6 Incidence and rate of hypoglycaemia during the treatment phase with ultra-rapid lispro (URLi) and Lispro in people with type 1 and type 2 diabetes

	Type 1 diabetes, PRONTO-T1D (N = 1222)						Type 2 diabetes, PRONTO-T2D, (N = 673)						Type 1 diabetes, PRONTO-Pump-2 (N = 432)					
	Incidence, %		Rate, events/patient/year				Incidence, %		Rate, events/patient/year				Incidence, %		Rate, events/patient/year			
	Mealt ime URLi	Lispro	Postmeal URLi	Lispro	Mealt ime URLi	Lispro	URLi	Lispro	URLi	Lispro	URLi	Lispro	URLi	Lispro	URLi	Lispro	URLi	Lispro
Severe hypoglycaemia	5.64	5.76	4.70	0.18	0.16	0.14	1.04	1.92	0.02	0.04	1.63	1.15	0.06	0.03				
Documented	88.2	90.4	90.5	13.5	12.5	14.2	74.6	78.3	7.57	7.43	84.4	85.6	24.6*	30.7*				
Nocturnal	31.5	32.8	30.5	1.75	1.25	1.24	18.8	16.4	0.68	0.53	45.8	53.4	4.24	4.31				
Non-nocturnal	75.1	74.4	78.0	8.88	8.13	9.85	52.4	49.9	3.92	3.20	81.6	80.1	20.4*	26.3*				
Postmeal hypoglycaemia																		
0-2 h	53.4	53.2	52.6	3.41	3.79	3.54	40.5*	29.1*	2.47	1.86	44.4	43.8	5.49	6.94				
0-4 h	69.8	69.6	73.5	6.25	6.65	7.18	50.0	43.3	3.51*	2.58*	62.1	60.3	12.5*	16.3*				
>4 h	45.5	51.4	50.5	4.35*	2.72*	3.88	26.0	27.4	1.10	1.15	52.3	59.0	10.5	11.6				

Incidence data are least squares means; rate data are aggregate rate.

*P < .05.

may be contributing factors. In CSII, cannula length may also play a role.⁴⁰ Further studies seeking to better understand causes for the increased injection and infusion site reactions with URLi are ongoing (NCT05067270).

5.3 | Pump compatibility

URLi's use in CSII was evaluated in two trials using the Medtronic MiniMed 530G, 630G, 640G, Paradigm Revel and Paradigm Veo.^{39,40} In both trials, the mean time interval to infusion set changes, and the rate of planned/routine infusion set changes, were similar between URLi and Lispro groups. The overall rate of unplanned/premature infusion set changes was higher with URLi compared with Lispro. This was primarily driven by a higher rate of infusion set changes because of infusion site reactions.^{39,40} This difference was small in both trials, averaging one additional infusion set change every 4 months based on routine changes every 3 days. The rates of premature infusion set changes as a result of an infusion set problem, occlusions or unexplained hyperglycaemia were similar between groups.

5.4 | Safety summary

- The incidence and rate of severe hypoglycaemia were similar between URLi and Lispro across trials.
- Postmeal hypoglycaemia occurred at a lower rate with URLi compared with Lispro beyond 4 hours postmeal, in line with its shorter duration of action, and at a higher rate within the first 4 hours postmeal, commensurate with its earlier onset of action.
- Treatment-emergent injection/infusion site reactions were more frequent with URLi, but were mostly mild or moderate in severity.
- The overall rate of premature infusion set changes was higher with URLi treatment, driven by a higher rate of infusion set changes because of infusion site reactions; rates of premature infusion set changes because of unexplained hyperglycaemia and occlusions were similar.

6 | PRACTICAL CONSIDERATIONS

URLi has a quick onset of action and a shorter duration of action than conventional insulin lispro, exhibiting a left-shift in its concentration-time and glucose-lowering profiles, with subsequent improvement in glycaemic control after meals. Individuals using CGM, who can view real-time glycaemic changes and predicted glycaemic data, can take further advantage of this technology to fine-tune their dosing and administer correction boluses when needed. In the PRONTO-T1D CGM substudy, CGM revealed that overnight glycaemic control was not optimal, with increasing blood glucose levels seen from evening to early morning. This could be improved with correction dosing. Correction dosing, while common, must be carried out safely, to avoid insulin stacking and an increased risk of hypoglycaemia. The advantage that

TABLE 7 Incidence of adverse events from randomization to end of the treatment phase with ultra-rapid lispro (URLi) and Lispro in people with type 1 and type 2 diabetes

	Type 1 diabetes, PRONTO-T1D			Type 2 diabetes, PRONTO-T2D		Type 1 diabetes, PRONTO-Pump-2	
	URLi (N = 451)	Lispro (N = 442)	Postmeal URLi (N = 329)	URLi (N = 336)	Lispro (N = 337)	URLi (N = 215)	Lispro (N = 217)
Deaths	1 (0.2)	1 (0.2)	0	2 (0.6)	1 (0.3)	0	0
Serious adverse events	36 (8.0)	40 (9.0)	24 (7.3)	26 (7.7)	25 (7.4)	13(6.0)	9 (4.1)
Severe hypoglycaemia	25 (5.5)	25 (5.7)	15 (4.6)	3 (0.9)	6 (1.8)	3 (1.4)	2 (0.9)
Discontinuation from study because of an adverse event	1 (0.2)	1 (0.2)	1 (0.3)	3 (0.9)	2 (0.6)	7 (3.3)	1 (0.5)
Discontinuation from study treatment because of an adverse event	6 (1.3)	5 (1.1)	5 (1.5)	6 (1.8)	3 (0.9)	13 (6.0)	2 (0.9)
Treatment-emergent adverse events	264 (58.5)	251 (56.8)	181 (55.0)	203 (60.4)	194 (57.6)	130 (60.5)	97 (44.7)
Treatment-emergent injection/infusion site reactions	13 (2.9)	1 (0.2)	8 (2.4)	9 (2.7)	0	81 (37.7)	22 (10.1)
Injection/infusion site reactions reported by ≥1% of participants							
Injection/infusion site reaction	7 (1.6)	1 (0.2)	4 (1.2)	NA	NA	41 (19.1)	15 (6.9)
Injection/infusion site pain	5 (1.1)	0	3 (0.9)	5 (1.5)	0	34 (15.8)	6 (2.8)

Note. Data are number of participants (%).

URLi has over other RAIs is that it has a shorter duration of action, meaning that it leaves the system earlier. As such, following the prescribed bolus doses and utilizing correction boluses where appropriate can probably be performed safely with URLi treatment, without increasing the risk of hypoglycaemia. Automated correction dose delivery via closed loop systems may be beneficial, particularly for tackling night-time hyperglycaemia with URLi. It is also probable that the enhanced pharmacokinetic properties that URLi exhibits increase its potential for improved glycaemic control with closed loop systems. Closed loop systems, while showing benefit in terms of improved glycaemic control and reduced hypoglycaemia, may be limited by the slower rate of absorption and longer duration of action that RAIs have. URLi's insulin time action and ability to reduce PPG excursions significantly without increasing hypoglycaemia could further enhance the benefits already observed with closed loop systems. Further studies are needed to confirm this.

Currently, URLi is approved for use in adults with type 1 or type 2 diabetes. Data on URLi treatment in paediatrics and adolescents are expected in 2022. Where indicated, switching from other insulins to URLi can be performed 1:1 unit; however, some adjustments may be needed, with consideration of individual characteristics, glycaemic targets, diet and lifestyle.

7 | CONCLUSIONS

URLi shows the fastest onset of action and shortest exposure duration of all the available insulins for subcutaneous injection. With a quicker onset of action, URLi can be administered at the start of the meal as opposed to several minutes before the meal. The earlier onset

of action with URLi treatment translates to similar long-term glycaemic control to Lispro but produces superior benefits in PPG management. Compared with Lispro, URLi provides superior PPG control in both type 1 and type 2 diabetes and reduces glucose excursions following meal consumption. Compared with Lispro, Faster aspart and Aspart, glucose concentrations in the early postmeal period are more comparable between people treated with URLi and PwD. In addition to superior PPG reduction with URLi, the rate of hypoglycaemia is similar between URLi and Lispro. Additional benefit is seen in type 1 diabetes, where postmeal hypoglycaemia is significantly reduced with URLi in the late postmeal period. More frequent, but predominantly mild, localized reactions seen with URLi are still under investigation.

Given its improved insulin time action profile, URLi helps to reduce the burden for people in need of intensive insulin therapy. URLi shows incremental clinical benefit over lispro, mainly in controlling postmeal glucose excursions, with no overall change in hypoglycaemic risk, therefore possibly providing less disruption to mealtime routines for PwD.

AUTHOR CONTRIBUTIONS

T.H. contributed to conception of the work, acquisition of data, interpretation of data, drafting and critical revision of the manuscript. C.P.O. contributed to conception of the work, interpretation of the data, drafting of the manuscript and critically reviewing the manuscript. R.J. contributed to the design of the work and critical revision of the manuscript. A.R. contributed to conception of the work, data acquisition and interpretation, and to critical revision of the manuscript. F.C. contributed to interpretation of the data, drafting of the manuscript and critically reviewing the manuscript. T.B. contributed to

conception of the work, acquisition of data, interpretation of data, drafting and critical revision of the manuscript.

ACKNOWLEDGEMENTS

This study was funded by Eli Lilly and Company.

CONFLICT OF INTEREST

T.H. is an employee of Profil; his institution received research grants from Adocia, Astra Zeneca, Biocon, Boehringer Ingelheim, Crinetics, Eli Lilly and Company, Gan & Lee Pharmaceuticals, Genova, Nestlé, Neuraly, Novo Nordisk, Sanofi and Zealand Pharma. T.H. reports that he received speaker honoraria from Eli Lilly and Company, Gan & Lee Pharmaceuticals, Mylan and Novo Nordisk. C.P.O., R.J., A.R. and F.C. are employees and minor stockholders of Eli Lilly and Company. T.B. received research grants from Abbott, Dexcom, Eli Lilly and Company, and Novo Nordisk, and speaker honoraria from Astra Zeneca, Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk and Viatrix. No other potential conflicts of interest relevant to this article were reported.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14773>.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Tim Heise  <https://orcid.org/0000-0002-8346-2037>

Thomas Blevins  <https://orcid.org/0000-0003-3746-9606>

REFERENCES

- Centers for Disease Control and Prevention. National Diabetes Statistics Report; 2020.
- Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D exchange in 2016-2018. *Diabetes Technol Ther.* 2019;21(2):66-72.
- McKnight JA, Wild SH, Lamb MJ, et al. Glycaemic control of type 1 diabetes in clinical practice early in the 21st century: an international comparison. *Diabet Med.* 2015;32(8):1036-1050.
- Overmann H, Heinemann L. Injection-meal interval: recommendations of diabetologists and how patients handle it. *Diabetes Res Clin Pract.* 1999;43(2):137-142.
- Datye KA, Boyle CT, Simmons J, et al. Timing of meal insulin and its relation to adherence to therapy in type 1 diabetes. *J Diabetes Sci Technol.* 2018;12(2):349-355.
- Berger M. Towards more physiological insulin therapy in the 1990s. A comment. *Diabetes Res Clin Pract.* 1989;6(4):S25-S31.
- Eli Lilly & Company. Humalog Prescribing Information. USPI; 2019.
- Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care.* 2019;42(8):1593-1603.
- Martens TW, Bergenstal RM, Pearson T, et al. Making sense of glucose metrics in diabetes: linkage between postprandial glucose (PPG), time in range (TIR) & hemoglobin A1c (A1C). *Postgrad Med.* 2021;133(3):253-264.
- Olczuk D, Priefer R. A history of continuous glucose monitors (CGMs) in self-monitoring of diabetes mellitus. *Diabetes Metab Syndr.* 2018;12(2):181-187.
- Liao B, Chen Y, Chigutsa F, Piras de Oliveira C. Fasting and postprandial plasma glucose contribution to glycated haemoglobin and time in range in people with type 2 diabetes on basal and bolus insulin therapy: results from a pooled analysis of insulin lispro clinical trials. *Diabetes Obes Metab.* 2021;23(7):1571-1579.
- Valensi P, Husemoen LLN, Weatherall J, Monnier L. Association of postprandial and fasting plasma glucose with HbA1c across the spectrum of glycaemic impairment in type 2 diabetes. *Int J Clin Pract.* 2017;71(12):e13041.
- Ketema EB, Kibret KT. Correlation of fasting and postprandial plasma glucose with HbA1c in assessing glycemic control; systematic review and meta-analysis. *Arch Public Health.* 2015;73:43.
- Monnier L, Colette C, Owens D. Postprandial and basal glucose in type 2 diabetes: assessment and respective impacts. *Diabetes Technol Ther.* 2011;13(Suppl 1):S25-S32.
- Lefever E, Vliebergh J, Mathieu C. Improving the treatment of patients with diabetes using insulin analogues: current findings and future directions. *Expert Opin Drug Saf.* 2021;20(2):155-169.
- Riddle MC. Basal glucose can be controlled, but the prandial problem persists-It's the next target! *Diabetes Care.* 2017;40(3):291-300.
- Madsbad S. Impact of postprandial glucose control on diabetes-related complications: how is the evidence evolving? *J Diabetes Complications.* 2016;30(2):374-385.
- Guideline for management of postmeal glucose in diabetes. *Diabetes Res Clin Pract.* 2014;103(2):256-268.
- Mannucci E, Monami M, Lamanna C, Adalsteinsson JE. Post-prandial glucose and diabetic complications: systematic review of observational studies. *Acta Diabetol.* 2012;49(4):307-314.
- Ceriello A. Postprandial hyperglycemia and diabetes complications: is it time to treat? *Diabetes.* 2005;54(1):1-7.
- Rawlings AM, Sharrett AR, Mosley TH, Ballew SH, Deal JA, Selvin E. Glucose peaks and the risk of dementia and 20-year cognitive decline. *Diabetes Care.* 2017;40(7):879-886.
- Abbatecola AM, Rizzo MR, Barbieri M, et al. Postprandial plasma glucose excursions and cognitive functioning in aged type 2 diabetics. *Neurology.* 2006;67(2):235-240.
- Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329(14):977-986.
- Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of endocrinology on the comprehensive type 2 diabetes management algorithm - 2018 executive summary. *Endocr Pract.* 2018;24(1):91-120.
- Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract.* 2017;23(Suppl 2):1-87.
- Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia.* 2021;44:1-44.
- Pratt E, Leohr J, Heilmann C, Johnson J, Landschulz W. Treprostinil causes local vasodilation, is well tolerated, and results in faster absorption of insulin Lispro. *Diabetes.* 2017;66:A253.
- Michael M, Zhang C, Siesky A, et al. Exploration of the mechanism of accelerated absorption for a novel insulin Lispro formulation. *Diabetes.* 2017;66(1):A250.
- Paavola C, Cox A, Sperry A, et al. A stable hexameric, ultra-rapid insulin formulation containing citrate. *Diabetes.* 2017;66(1):A254.

30. Leohr J, Dellva MA, Carter K, LaBell E, Linnebjerg H. Ultra rapid Lispro (URLi) accelerates insulin Lispro absorption and insulin action vs Humalog® consistently across study populations: a pooled analysis of pharmacokinetic and Glucodynamic data. *Clin Pharmacokinet.* 2021;60:1423-1434.
31. Kazda C, Leohr J, Liu R, et al. Ultra rapid lispro (URLi) shows accelerated pharmacokinetics and greater reduction in postprandial glucose versus Humalog(R) in patients with type 1 diabetes mellitus in a randomized, double-blind meal test early-phase study. *Diabetes Obes Metab.* 2022;24(2):196-203.
32. Leohr J, Kazda C, Liu R, et al. Ultra-rapid lispro shows faster pharmacokinetics and reduces postprandial glucose excursions versus Humalog(R) in patients with type 2 diabetes mellitus in a randomized, controlled crossover meal test early phase study. *Diabetes Obes Metab.* 2022;24(2):187-195.
33. Kazda C, Leohr J, Liu R, et al. Ultra rapid Lispro (URLi) shows faster absorption of insulin lispro vs Humalog® during insulin pump (CSII) use in patients with T1D. *Diabetes.* 2018;67:1006.
34. Heise T, Linnebjerg H, Coutant D, et al. Ultra rapid lispro lowers postprandial glucose and more closely matches normal physiological glucose response compared to other rapid insulin analogues: a phase 1 randomized, crossover study. *Diabetes Obes Metab.* 2020;22(10):1789-1798.
35. Klaff L, Cao D, Dellva MA, et al. Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: results from the 26-week PRONTO-T1D study. *Diabetes Obes Metab.* 2020;22(10):1799-1807.
36. Bue-Valleskey J, Klaff L, Cho JI, et al. Long-term efficacy and safety of ultra rapid Lispro (URLi) in adults with type 1 diabetes: the PRONTO-T1D extension. *Diabetes Ther.* 2021;12(2):569-580.
37. Malecki MT, Cao D, Liu R, et al. Ultra-rapid Lispro improves postprandial glucose control and time in range in type 1 diabetes compared to Lispro: PRONTO-T1D continuous glucose monitoring substudy. *Diabetes Technol Ther.* 2020;22(11):853-860.
38. Blevins T, Zhang Q, Frias JP, Jinnouchi H, Chang AM. Randomized double-blind clinical trial comparing ultra rapid Lispro with Lispro in a basal-bolus regimen in patients with type 2 diabetes: PRONTO-T2D. *Diabetes Care.* 2020;43(12):2991-2998.
39. Bode BW, Garg SK, Norwood P, et al. Compatibility and safety of ultra rapid Lispro with continuous subcutaneous insulin infusion in patients with type 1 diabetes: PRONTO-pump study. *Diabetes Technol Ther.* 2021;23(1):41-50.
40. Warren M, Bode B, Cho JI, et al. Improved postprandial glucose control with ultra rapid lispro versus lispro with continuous subcutaneous insulin infusion in type 1 diabetes: PRONTO-Pump-2. *Diabetes Obes Metab.* 2021;23(7):1552-1561.
41. Bode BW, Carlson A, Liu R, et al. Ultra rapid Lispro demonstrates similar time in target range to Lispro with a hybrid closed-loop system. *Diabetes Technol Ther.* 2021;23:828-836.
42. Hsu L, Buckingham B, Basina M, et al. Fast-acting insulin Aspart use with the MiniMed(TM) 670G system. *Diabetes Technol Ther.* 2021;23(1):1-7.
43. Boughton CK, Hartnell S, Thabit H, et al. Hybrid closed-loop glucose control with faster insulin aspart compared with standard insulin aspart in adults with type 1 diabetes: a double-blind, multicentre, multinational, randomized, crossover study. *Diabetes Obes Metab.* 2021;23(6):1389-1396.
44. Ozer K, Cooper AM, Ahn LP, Waggonner CR, Blevins TC. Fast acting insulin Aspart compared with insulin Aspart in the Medtronic 670G hybrid closed loop system in type 1 diabetes: an open label crossover study. *Diabetes Technol Ther.* 2021;23(4):286-292.
45. Bowering K, Case C, Harvey J, et al. Faster Aspart versus insulin Aspart as part of a basal-bolus regimen in inadequately controlled type 2 diabetes: the onset 2 trial. *Diabetes Care.* 2017;40(7):951-957.
46. Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin Aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1). *Diabetes Care.* 2017;40(7):943-950.

How to cite this article: Heise T, Piras de Oliveira C, Juneja R, Ribeiro A, Chigutsa F, Blevins T. What is the value of faster acting prandial insulin? Focus on ultra rapid lispro. *Diabetes Obes Metab.* 2022;24(9):1689-1701. doi:[10.1111/dom.14773](https://doi.org/10.1111/dom.14773)